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Levetiracetam in refractory epilepsy: a prospective observational study

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KEYWORDS
Levetiracetam;
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Summary This prospective open-label study used flexible dosing schedules of levetiracetam (LEV) in patients with refractory epilepsy attending a single centre to explore its effectiveness in everyday clinical practice.

One hundred and fifty-six patients with uncontrolled localisation-related or idiopathic-generalised epilepsy were prescribed adjunctive LEV following a 3-month baseline. The primary end points were seizure freedom for at least 6 months, $\geq$50% reduction (responder) or $<$50% reduction for 6 months, or discontinuation of LEV due to lack of efficacy, adverse effects or both.

Overall, 40 (26%) patients became seizure free on adjunctive LEV, including 8 (40%) with idiopathic-generalised epilepsy. Twenty-five (63%) of the seizure-free patients took 1000 mg LEV per day or less. A further 33 (21%) patients were classified as responders.

LEV was withdrawn in 46 (29%) patients (27 adverse effects, 8 lack of efficacy, 11 both). Intolerable sedation, reported by 20 (13%) patients, was the commonest complaint leading to treatment failure. Behavioural side effects led to LEV withdrawal in 7 (5%) patients.

LEV is an effective adjunctive treatment for refractory idiopathic and localisation-related epilepsies. Many patients who responded optimally to LEV did so at 1000 mg per day or less.
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Introduction

Levetiracetam (LEV) is a novel antiepileptic drug (AED), which was licensed in the UK in November 2000 as an adjunctive treatment for partial seizures with or without secondary generalisation. Its mechanisms of action appear different from other AEDs.[1] LEV binds to a specific membrane-binding site in the brain.[2] It does not affect glutamate or gamma aminobutyric acid-mediated synaptic transmission,[3,4] nor does it modulate voltage dependent sodium or T-type calcium currents.[5] LEV showed no efficacy in maximal electroshock and chemoconvulsive seizure models,[6] but markedly suppressed seizures in kindled and genetically epileptic animals.[7,8] Its pharmacokinetic characteristics have been described as close to ideal.[9] LEV has high oral bioavailability unaffected by food, exhibits linear kinetics, is not significantly bound to plasma proteins, is largely excreted unchanged by the kidneys, and is not prone to pharmacokinetic drug interactions.

The efficacy of LEV has been assessed in placebo-controlled randomised trials which demonstrated reduction in seizure numbers and improved quality

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of life in patients with partial seizures with or without secondary generalisation.[10–14] Post-marketing studies have suggested that LEV may also be efficacious for idiopathic-generalised epilepsies.[15–17] Randomised-controlled trials carried out to meet regulatory requirements provide little information to guide pharmacological decision-making in clinical practice.[18] Pragmatic open-label studies in the post-marketing phase employing flexible dosing schedules will allow the effectiveness of an AED to be assessed in ''real life'' situations. We conducted a single centre, prospective, open-label study of adjunctive LEV in patients with uncontrolled seizures to assess its utility for a variety of seizure disorders in everyday clinical practice.

Methods

One hundred and fifty-six patients (70 males, 86 females; median age 38 years, range 16–78 years) attending the Epilepsy Clinic at the Western Infirmary in Glasgow, Scotland with uncontrolled epilepsy of any type were recruited into the study. One hundred and thirty-six patients had localisation-related epilepsy (119 partial and secondary generalized seizures, 17 partial seizures only) and 20 had idiopathic generalized epilepsy (11 juvenile myoclonic epilepsy, 5 typical absences and tonic–clonic seizures, 4 tonic–clonic seizures only). Patients had already failed treatment with a median of three AEDs (range 1–9). Seventy-seven (49%) patients were taking 1, 68 (44%) 2, 10 (6%) 3 and 1 (1%) patient 4 concomitant AEDs at the time of entry into the study.

Patients underwent baseline evaluation for 3 months, during which seizure types and frequencies were recorded and AED schedules remained unchanged. Median seizure frequency during the baseline period was 5 per month (range 1 to 120 per month). Patients were reviewed by the same clinician every 6 weeks or sooner if required. Standard forms were used to collect seizure numbers and document adverse effects.

Three starting doses were employed in the study. The manufacturer's recommended schedule of 500 mg twice daily was used in 58 patients, 500 mg once daily was prescribed for 49 patients and the remaining 49 patients took an initial 250 mg LEV once daily. Dosage modifications were made in increments of 250–500 mg daily every 2–4 weeks depending on clinical response and adverse effects. When seizure freedom was attained at any dose, no further modification was made to the regimen. Withdrawal of concomitant AEDs was attempted in seizure-free patients only if the combined drug burden was thought to be responsible for intolerable adverse effects.

The primary end points were seizure freedom for at least 6 months on an unchanged dose of LEV, $\geq$50% reduction (responder) or $<$50% reduction (marginal effect) in monthly seizure frequency for 6 months compared to baseline at maximally tolerated LEV doses, or discontinuation of LEV due to lack of efficacy, adverse effects or both. Data were analysed using Minitab for Windows statistical software. Proportions were expressed as percentages. Ranges were quoted with medians or means and standard deviations as appropriate. The Mann-Whitney test was used to compare non-parametric continuous data and χ^2 test was used for categorical data.

Results

Overall, 40 (26%) of the 156 patients became seizure free for a minimum of 6 months on an unchanged dose of LEV and a further 33 (21%) could be classed as responders. AED combinations in the seizure-free patients are listed in Table 1. No particular combination appeared more efficacious or more likely to cause adverse effects than the others. Thirty-seven (24%) patients reported $<$50% in seizure frequency, but elected to continue treatment with the drug. LEV was withdrawn in 46 (29%) patients, 27 (17%) because of adverse effects, 8

Table 1 Treatment schedules producing seizure freedom.

Schedules	Patient numbers	Antiepileptic drugs
LEV monotherapy	1	LEV
One other AED	16	LEV/CBZ
	4	LEV/VPA
	3	LEV/LTG
	1	LEV/GBP
Two other AEDs	15	LEV/CBZ/TPM
	3	LEV/LTG/VPA
	2	LEV/CBZ/GBP
	1	LEV/LTG/TPM
Three other AEDs	1	LEV/CBZ/CLB/TPM
	1	LEV/LTG/TPM/VPA
Four other AEDs	1	LEV/AZM/LTG/PB/VPA

Abbreviations: AEDs, antiepileptic drugs; LEV, levetiracetam; CBZ, carbamazepine; VPA, sodium valproate; LTG, lamotrigine; GBP, gabapentin; TPM, topiramate; CLB, clobazam; AZM, acetazolamide; PB, phenobarbital.

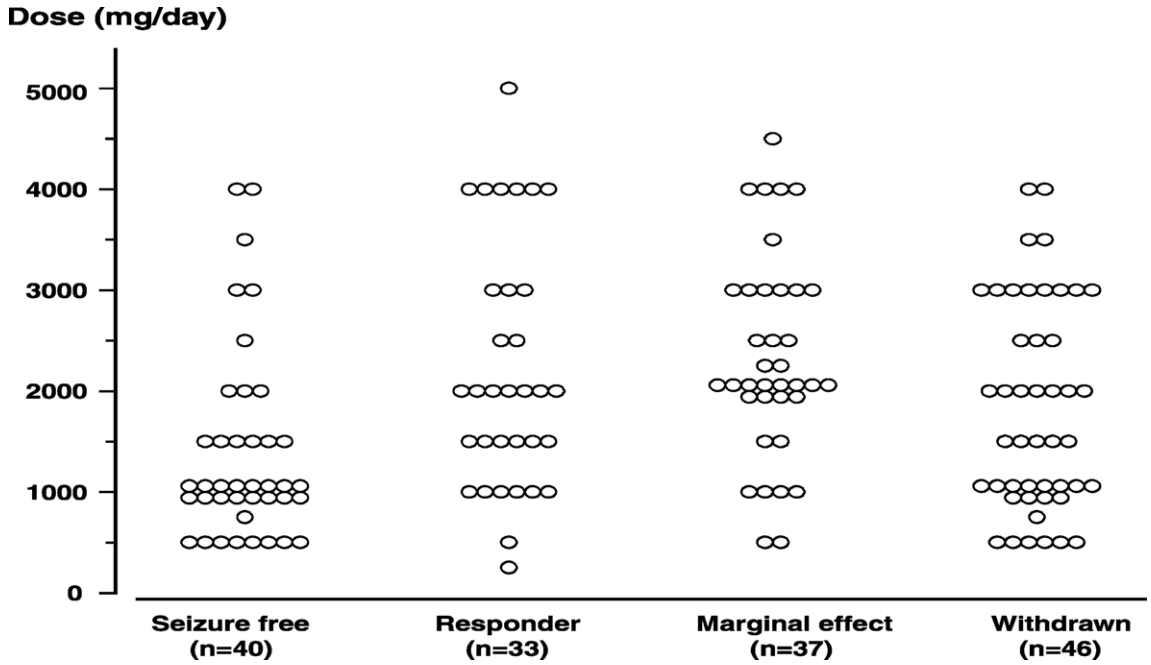

Figure 1 Daily levetiracetam doses in each outcome group. Responder ≥50% seizure reduction. Marginal effect <50% seizure reduction.

(5%) due lack of efficacy, and 11 (7%) due to a combination of lack of efficacy and side effects.

There was no correlation between LEV doses and clinical responses (Fig. 1). The median daily doses in the four main outcome groups were: 1000 mg in seizure-free patients, 2000 mg in responders and in patients reporting a <50% seizure reduction, and 1500 mg in patients in whom LEV was withdrawn. Interestingly, 25 (63%) of the 40 patients who became seizure free with adjunctive LEV were taking 1000 mg per day or less with 8 being controlled on just 500 mg daily.

Outcomes by type of epilepsy are shown in Table 2. Patients with idiopathic-generalised epilepsy appeared to respond to adjunctive LEV with 40% becoming seizure free and a further 25% being classified as responders. Juvenile myoclonic epilepsy ($n = 11$) was the most common syndrome in this cohort with five of these patients attaining seizure freedom. Three patients were converted to LEV monotherapy. One remained seizure free, while another developed adverse effects and had LEV withdrawn. The third patient reported only a marginal response to LEV, but had an improved side effect profile and elected to continue treatment.

Of the 46 patients in whom LEV was withdrawn, 38 reported adverse effects (Table 3). Sedation ($n = 20$) was the commonest complaint leading to failure of LEV treatment. Behavioural problems including aggression, depression, emotional lability and emergence of post-ictal psychosis and hallucinations were reported by eight patients and led

Table 2 Outcomes in different seizure types and epilepsy syndromes.

	Seizure free	Responder	Marginal effect	Withdrawn	Total
Idiopathic-generalised epilepsies	8	5	5	2	20
Juvenile myoclonic epilepsy	5	3	3	0	11
Absences ± tonic–clonic seizures	2	2	1	0	5
Generalised tonic–clonic seizures only	1	0	1	2	4
Localisation-related epilepsies	32	28	32	44	136
Partial seizures only	2	4	3	8	17
Partial seizures with secondary generalisation	30	24	29	36	119
Grand total	40	33	37	46	156

Responder: ≥50% seizure reduction vs. baseline. Marginal effect: <50% seizure reduction vs. baseline.

Table 3 Side effects reported by patients on adjunctive levetiracetam.

Side effect	Patients reporting	Patients withdrawn
Sedation	27	20
Fatigue	8	4
Headache	5	4
Worsening seizures	4	4
Aggression	4	3
Nausea	2	2
Depression	1	1
Diarrhoea	1	1
Dizziness	1	1
Emotional lability	1	1
Episodic leg weakness	1	1
Post-ictal psychosis	1	1
Hallucinations	1	1
Weight gain	1	1
Ataxia	1	0
Insomnia	1	0
Tremor	1	0
Total number of patients*	50	38

* Some patients reported more than one side effect.

to LEV withdrawal in seven of these. Four patients with localisation-related epilepsy reported worsening of seizures. Treatment with LEV did not demonstrate an overall effect on body weight. While individual patients gained and lost weight over the course of the study (range −6.2 to +6.4 kg), the mean change in the entire cohort was +0.09 kg (S.D. ± *2.03* kg). No significant differences in the incidence of adverse effects or withdrawal rates were observed with the three different starting doses. Overall, 71% patients continued on treatment with LEV (Fig. 2).

Discussion

There are convincing epidemiological data to suggest that more than 30% of patients with newly diagnosed epilepsy never achieve lasting remission with currently available AEDs.[19–22] There is, therefore, a clear need for new AEDs with novel mechanisms of action.[23] With its unique pharmacological profile LEV offers a valuable addition to the therapeutic armamentarium for the treatment of refractory epilepsy.[24] Data from open-label pragmatic studies will enable the most effective dose ranges and titration schedules to be identified.

LEV appeared to be highly efficacious with 26% of our patients achieving complete control of seizures for 6 months or more. The doses producing seizure freedom were generally modest with 63% of patients responding to 1000 mg per day or less. This was significantly lower than those noted in the other outcome groups, suggesting that LEV or AED combinations containing LEV may have had a specific effect on the epileptic process in these individuals. We attempted withdrawal to LEV monotherapy in just three patients, one of whom remained seizure free.

Patients with idiopathic generalized epilepsy appeared to respond to adjunctive LEV with 40% becoming seizure free. Those with juvenile myoclonic

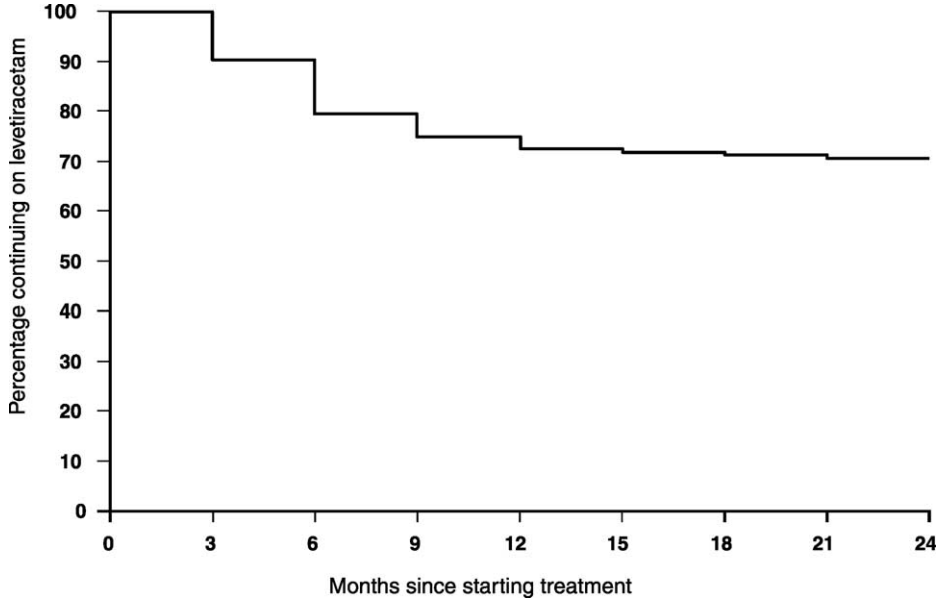

Figure 2 Actuarial estimate of time to withdrawal.

epilepsy fared especially well with 45% achieving seizure freedom. Previous treatment with a median of three AEDs had failed to control myoclonic jerks and tonic—clonic seizures in these patients. These results suggest that LEV could be a useful agent for the treatment of myoclonic syndromes.

Overall, 17% patients developed adverse effects requiring discontinuation of LEV and a further 12% had the drug withdrawn after titration due to a combination of lack of efficacy and side effects. Sedation was the most common complaint. However, 5% patients developed behavioural problems requiring withdrawal of LEV. These included aggression, depression, mood swings, hallucinations, and post-ictal psychosis, all of which have been reported previously with this drug.[25]

Conclusions

LEV has the potential to produce seizure freedom in a significant proportion of patients with hitherto refractory epilepsy. Sedation and the emergence of behavioural problems were the main side effects leading to LEV discontinuation.

Acknowledgements

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